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[19] The State Intellectual Property Office of the People's Republic of China [51] Int. Cl[6]

A61K 31/70

A01N 45/00

[12] Published Specification of Application for Patent for Invention

[21] Application No. 98108347.1

[43] Date of Publication: April 28, 1999

[11] Publication No. CN 1214909A

[22] Date of Filing: May 14, 1998

[21] Application No. 98108347.1

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Claims: 1 page Description: 7 pages

Drawings: 0 page

[54] **Title of Invention:**

A composite formulation of veterinary antiparasitic

[57] **Abstract:**

The present invention provides a composite formulation of veterinary antiparasitic, characterized in that a complex antiparasitic preparation containing the components of Avermectin or Ivermectin mixed with Albendazole is prepared as an oral powder, oral capsules, oral tablets, an oral paste, an oral suspension, an oral emulsion, an injection emulsion, and an oil injection. The veterinary antiparasitic of the present invention not only has strong helminthicide effects against nematodes in vivo and parasites in vitro in animals, but also has good effects against the dosage cephalocysts and trematodes, so it has an expanded parasiticidal spectrum and reduces times to be administered to animals and lowers costs.

ISSN1008-4274

Published by Intellectual Property Press

Claims

1. A veterinary antiparasitic containing Avermectin or Ivermectin, characterized in that a preparation containing the components of Avermectin or Ivermectin mixed with Albendazole is prepared as an oral powder, an oral capsule, an oral tablet, an oral paste, an oral suspension, an oral emulsion, an injection emulsion, and an oil injection solution, wherein the weight ratio of Avermectin or Ivermectin to Albendazole is 1:10-100.

2. The antiparasitic according to claim 1, characterized in that the components and contents of said oral powder (calculated with the powder weight as 100) are: 0.01-2% of Avermectin or Ivermectin, 0.5-99% of Albendazole, 0.01-0.1% of antioxidant, and the balance is a filler, and said antioxidant comprises dibutylhydroxytoluene and said filler comprises $CaCO_3$, starch, and soybean meal.

3. The antiparasitic according to claim 1, characterized in that the components and contents of said oral capsule are that each capsule contains 0.5-10mg of Avermectin or Ivermectin, 10-500mg of Albendazole, and the balance is a filler, and said filler comprises starch and $CaCO_3$.

4. The antiparasitic according to claim 1, characterized in that the components and contents of said oral tablet are that each tablet has 0.5-20mg of Avermectin or Ivermectin, 10-750mg

of Albendazole, and the balance is a vehicle, wherein said vehicle comprises starch, dextrin and magnesium stearate.

5. The antiparasitic according to claim 1, characterized in that the components and contents of the oral paste (calculated with the paste weight as 100) are: 0.01-2.5% of Avermectin or Ivermectin, 0.25-80% of Albendazole, 0-30% of calcium phosphate dibasic, 0-20% of $CaCO_3$, 10-30% of glycerol, 0.5-1.5% of sodium carboxymethycellulose, and 10-20% of water.

6. The antiparasitic according to claim 1, characterized in that the components and contents of said oral suspension (calculated with the suspension's weight as 100) are: 0.01-2% of Avermectin or Ivermectin, 0.5-60% of Albendazole, 0.1-3% of a stabilizer, 0.5-2% of a preservative, and the balance is water; wherein said stabilizer comprises sodium carboxymethycellulose and xanthan gum, and said preservative comprises phenylmethanol.

7. The antiparasitic according to claim 1, characterized in that the components and contents of said oral emulsion (calculated with the emulsion's weight as 100) are: 0.01-1.5% of Avermectin or Ivermectin, 0.5-30% of Albendazole, 2-30% of glacial acetic acid, 0.5-10% of a surfactant, 5-20% of glycerine, 5-20% of ethanol, 0.1-20% of a stabilizer, 0.5-2% of a preservative, an adequate amount of triethanolamine for adjusting pH value, and the balance is water; wherein said surfactant comprises Tween-80, said stabilizer comprises

sodium carboxymethycellulose and xanthan gum, and said preservative comprises phenylmethanol.

8. The antiparasitic according to claim 1, characterized in that the components and contents of said injection emulsion (calculated with the emulsion's weight as 100) are: 0.05-1.5% of Avermectin or Ivermectin, 2-25% of Albendazole, 2-20% of glacial acetic acid, 0.5-10% of a surfactant, 5-50% of glycerine, 5-50% of ethanol, an adequate amount of triethanolamine for adjusting pH value, and the balance is water; wherein said surfactant comprises Tween-80.

9. The antiparasitic according to claim 1, characterized in that the components and contents of said oily injection solution (calculated with the injection solution's weight as 100) are: 0.05-1.0% of Avermectin or Ivermectin, 2-10% of Albendazole, 0-10% of ethyl oleate, and the balance is sesame oil.

Description

A composite formulation of veterinary antiparasitic

The present invention relates to a veterinary antiparasitic, and more particularly to a composite veterinary antiparasitic preparation of Avermectin (AVM) or Ivermectin (IVM) mixed with Albendazole (ABDZ) formulated as an oral powder, capsules, tablets, a paste (or cream), a suspension, an emulsion, an injection emulsion, and an oily injection.

In the early 1980s, the American company MERCK successfully developed the two substances Avermectin and Ivermectin as veterinary antiparasitic, which had strong helminthicidal effects against both in vivo nematodes and in vitro parasites (acari, tick, lice, and fly larvae) in animals, but they do not have effects in expelling/killing cephalocyst and trematodes in vivo (William C. Campbell, Ivermectin and Abamectin, 1989, Springer-Verlag, New York Inc., P215-229).

Domestic fowls and animals such as pigs, cattle, sheep and goats, chickens, etc. are usually infected with nematodes, trematodes, cephalocyst and in vitro parasites at the same time, therefore, during the period of raising the animals, in order to ensure the normal growth of the fowls and animals, it is necessary to use helminthicide and antiparasitic against the in vitro parasites many times. Hitherto, there has not yet been

made available a single formulation of veterinary antiparasitic drug capable of expelling/killing the nematodes, trematodes, cephalocyst and in vitro parasites at the same time.

An object of the present invention is to overcome the problem in the prior art, and to provide a composite formulation veterinary antiparasitic which can expel and kill the nematodes, trematodes, cephalocyst and in vitro parasites at the same time.

The main technical solution of the present invention is to prepare a composite formulation of veterinary antiparasitic using Avermectin or Ivermectin mixed with Albendazole into the dosage form of an oral powder, capsules, tablets, a paste, a suspension, an emulsion, an injection emulsion, and an oily injection.

In the composite formulation of veterinary antiparasitic of AVM or IVM mixed with Albendazole prepared according to the present invention, the ratio of AVM or IVM to Albendazole is 1:10-100, preferably 1:40-60. Particular composition and contents of various preparations (calculated with the amount of the various preparations as 100%) are as following:

1. Oral powder

The composition and contents of the oral powder in the present invention are: 0.01-2% of AVM or IVM, 0.5-99% of

Albendazole, 0.01-0.1% of an antioxidant, and the balance is a filler.

Said AVM is the fermentation product of Streptomyces avermitilis and it is a mixture formed by eight homologs of very similar structures, and usually the mixture of B_{1a} and B_{1b} is used, which can be isolated with the existing techniques; and said IVM is the hydrogenated reduction product of Avermectin (William C. Campbell, "Ivermectin and Abamectin", Springer-Verlag New York Inc., 1989, P287-310).

Said Albendazole is a commercial product, which is a widely used anthelmintic having expelling/killing effects against the in vivo nematodes, trematode and cephalocyst, but it is inactive against in vitro parasites (acari, tick, lice, and fly larvae) and their larvae widely parasitized in animals (Yan Jiye, Drug Manual for Domestic Fowls and Stocks, the second edition, 1997, Jindun Press).

Said antioxidant comprises dibutylhydroxytoluene (BHT) and butylated hydroxyanisole, both of them are commercial products. Said filler comprises $CaCO_3$ and soybean meal.

2. Oral capsules

The components and contents of the oral capsules in the present invention are: each capsule containing 0.5-10mg of AVM or IVM, 10-500mg of Albendazole, and the balance is a filler.

Said filler comprises starch and $CaCO_3$.

3. Oral tablets

The components and contents of the oral tablets in the present invention are: each capsule containing 0.5-20mg of AVM or IVM, 10-750mg of Albendazole, and the balance is a vehicle.

Said vehicle comprises starch, dextrin and magnesium stearate.

4. Oral paste

The components and contents of the oral paste in the present invention are: 0.01-2.5% of AVM or IVM, 0.25-80% of Albendazole, 0-30% of calcium hydrophosphate, 0-20% of $CaCO_3$, 10-30% of glycerol, 10-20% of water, and 0.5-1.5% of sodium carboxymethycellulose.

5. Oral suspension

The components and contents of the oral suspension in the present invention are: 0.01-2% of AVM or IVM, 0.5-60% of Albendazole, 0.1-3% of a stabilizer, 0.5-2% of a preservative, and the balance is a vehicle.

Said stabilizer comprises sodium carboxymethycellulose and xanthan gum.

Said preservative comprises phenylmethanol.

6. Oral emulsion

The components and contents of the oral emulsion in the present invention are: 0.01-1.5% of AVM or IVM, 0.5-30% of Albendazole, 2-30% of glacial acetic acid, an adequate amount

of triethanolamine, 0.5-10% of a surfactant, 5-20% of glycerine, 5-20% of ethanol, 0.1-20% of a stabilizer, 0.5-2% of a preservative, and the balance is water.

Said surfactant comprises Tween-80.

Said stabilizer comprises sodium carboxymethycellulose and xanthan gum.

Said preservative comprises phenylmethanol.

Said triethanolamine is used to adjust the pH value of the oral emulsion.

7. Injection emulsion

The components and contents of the injection emulsion in the present invention are: 0.05-1.5% of AVM or IVM, 2-25% of Albendazole, 2-20% of glacial acetic acid, an adequate amount of triethanolamine, 0.5-10% of a surfactant, 5-50% of glycerol, 5-50% of ethanol, and the balance is water.

Said surfactant comprises Tween-80.

Said triethanolamine is used to adjust the pH value of the injection emulsion.

8. Oily injection solution for injection use

The components and contents of the oily injection in the present invention are: 0.05-1.0% of AVM or IVM, 2-10% of Albendazole, 0-10% of ethyl oleate, and the balance is sesame oil.

The eight preparations of the present invention are prepared and used in conventional ways.

The main advantages and effects of the present invention are as follows.

The present invention uses the composite formulation prepared by AVM or IVM mixed with Albendazole, which is capable of expelling and killing the nematodes, trematodes, cestodes and the in vitro parasites at the same time, so that the production costs and the number of times to use the drug are reduced, which is very convenient for farmers and veterinarians, and which is beyond what can be achieved by the current anthelmintic and antiparasitic for in vitro parasites, therefore it has an extensive market perspective.

The features of the present invention are further described by the following examples.

Example 1

In this example, an oral composite formulation powder containing 0.02% of AVM and 0.6% of Albendazole (W/W) was prepared.

0.022kg of AVM with a purity of 90% and 0.1kg of dibutylhydroxytoluene (BHT) were weighed up, introduced into a dissolving jar, and 500ml of medical ethanol were added to dissolve them, then the mixture was sprayed onto 0.63kg of Albendazole with a purity of 95% and stirred uniformly, then 100kg of maze starch were added, and they were stirred uniformly

in a compounding tank so as to obtain the oral composite formulation powder containing 0.02% of AVM and 0.6% of Albendazole.

Use and dosage: for expelling and killing parasitic helminth and in vitro parasites in cattle, goats and sheep, this powder was administered at 1g per 1kg body weight; for expelling and killing in vitro parasites in pigs: this powder was administered at 1.5g per 1kg body weight.

Example 2

In this example, an oral composite formulation powder containing 1.9% of IVM and 95% of Albendazole was prepared.

2.11kg of IVM with a purity of 90% and 0.02kg of butylated hydroxyarisol were weighed up, introduced into a dissolving jar, and 500ml of medical ethanol were added to dissolve them, then the mixture was sprayed onto 97.9kg of Albendazole with a purity of 95% and stirred uniformly, then $CaCO_3$ was added to 100kg, and then they were stirred uniformly in a compounding tank, so as to obtain an oral composite formulation powder containing 1.9% of IVM and 95% of Albendazole (W/W).

Use and dosage: for expelling and killing parasitic helminth and in vitro parasites in cattle, goats and sheep, 1g of this product was administered per 95kg body weight; for expelling and killing in vitro parasites in pigs: this product was administered at 1.5g per 95kg body weight.

Example 3

In this example, oral composite formulation capsules each containing 0.5mg of AVM and 50mg of Albendazole were prepared.

0.55kg of AVM with a purity of 90% were weighed, put into the dissolving jar and dissolved with 10L of acetic ether, then the mixture was agitated uniformly with 50kg of Albendazole, then $CaCO_3$ was added up to the total weight 200kg, agitated and vacuum dried, and finally distributed into 200mg capsules.

Use and dosage: for expelling and killing parasitic helminth and in vitro parasites in cattle, goats and sheep, one of the capsules was administered per 2.5kg body weight; for expelling and killing in vivo and in vitro parasites in pigs: 3 of the capsules were administered per 5kg body weight.

Example 4

In this example, oral composite formulation capsules each containing 9mg of IVM and 480mg of Albendazole were prepared.

9.9kg of IVM with a purity of 90% were weighed up, and introduced into a dissolving jar, 10L of acetic ether were added to dissolve it, then the mixture was mixed uniformly with 480kg of Albendazole, and then starch was added to 500kg and uniformly mixed, the mixture was vacuum dried, and charged with each capsule containing 500mg.

Use and dosage: for expelling and killing parasitic helminth and in vitro parasites in cattle, goats and sheep, one of the present capsules was administered per 45kg body weight; for expelling and killing in vivo and in vitro parasites in pigs: 3 of the present capsules were administered per 90kg body weight.

Example 5

In this example, oral composite formulation tablets each containing 1mg of IVM and 30mg of Albendazole were prepared.

0.11kg of IVM with a purity of 92% were weighed up, and introduced into a dissolving jar, 5L of medical ethanol were added to dissolve it, then it was sprayed onto 20kg of starch and mixed uniformly in a mixing jar, then 3kg of Albendazole, 10kg of dextrin and 2kg of magnesium stearate were added, stirred uniformly, granulated and pressed into tablets of 350mg each (containing 1mg of IVM and 30mg of Albendazole).

Use and dosage: for expelling and killing parasites (helminth) and in vitro parasites in goats and sheep, 1 tablet was used per 5kg body weight.

Example 6

In this example, oral composite formulation tablets each containing 15mg of IVM and 700mg of Albendazole were prepared.

15.6kg of IVM with a purity of 92% were weighed up, and introduced into a dissolving jar, 20L of medical ethanol were added to dissolve it, then it was sprayed onto 70kg of starch and mixed uniformly in a mixing jar, then 700kg of Albendazole, 20kg of dextrin and 10kg of magnesium stearate were added, stirred uniformly, granulated and pressed into tablets of 800mg each (containing 15mg of IVM and 750mg of Albendazole).

Use and dosage: for expelling and killing in vivo parasites (helminth) and in vitro parasites in goats and sheep, 1 tablet was used per 75kg body weight.

Example 7

In this example, an oral composite formulation paste containing 0.1% of AVM and 5.0% of Albendazole was prepared.

0.11kg of AVM with a purity of 92% were weighed up with 1L ethanol added in and it was dissolved with heating, then 30L of glycerol were added and mixed uniformly, then 5.3kg of Albendazole, 30kg of calcium hydrophosphate, and 20kg of calcium carbonate were added in, and then 100L of aqueous solution containing 1.5kg of carboxymethycellulose were added in and stirred uniformly. It was ground with a colloid mill after being agitated uniformly to obtain the oral composite formulation paste.

Use and dosage: for expelling and killing parasitic helminth and in vitro parasites in goats and sheep, 1g of the paste was

administered per 5kg body weight.

Example 8

In this example, an oral composite formulation paste containing 2.5% of IVM and 75% of Albendazole was prepared.

2.7kg of IVM with a purity of 92% were weighed up, with 3L of ethanol added in to dissolve it with heating, then 10L of glycerol was added, mixed uniformly and then 75kg of Albendazole and 2kg of phosphonic acid were added in succession, and then an aqueous solution containing 0.5kg of carboxymethycellulose was added in to 100L and stirred uniformly. It was ground with a colloid mill to obtain the oral composite formulation paste.

Use and dosage: for expelling and killing in vivo parasites (helminth) and in vitro parasites in goats and sheep, 0.2g of the paste were used per 25kg body weight.

Example 9

In this example, an oral composite formulation suspension containing 0.02% of AVM and 1% of Albendazole was prepared.

0.022kg of AVM with a purity of 90% were weighed up with 0.5L ethanol added in to dissolve it, then 20L of 1,2-propylene glycol, 0.05L of phenylmethanol, and 1kg of Albendazole were added, then a solution of 0.3% xanthan gum was added to make it up to 100L, which was stirred uniformly and ready for use.

Use and dosage: for expelling and killing in vivo parasitic helminth and in vitro parasites in goats and sheep, 1ml thereof was administered per 1kg body weight.

Example 10

In this example, an oral composite formulation suspension containing 1.8% of IVM and 60% of Albendazole was prepared.

2.0kg of IVM with a purity of 90% were weighed up with 1L of ethanol added in to dissolve it, then 20L of 1,2-propylene glycol, 1L of phenylmethanol, and 60kg of Albendazole were added, then a solution of 2.5% sodium carboxymethycellulose was added in to make it up to 100L, which was stirred uniformly and then ready for use.

Use and dosage: for expelling and killing in vivo parasites (helminth) and in vitro parasites in goats and sheep, 1ml thereof was used per 90kg body weight.

Example 11

In this example, an oral composite formulation emulsion containing 0.05% of AVM and 2.5% of Albendazole was prepared.

0.055kg of AVM with a purity of 90% were taken and put in a dissolving jar to be dissolved by adding 2L of ethanol to obtain a solution A. 2.55kg of Albendazole were taken and dissolved in 28L of glacial acetic acid, then triethanolamine

was used to adjust its pH value to 4 to 5, then 2kg of Tween-80 were added and mixed uniformly, and then 7kg of glycerine and 2kg of phenylmethanol were added to obtain a solution B, and the solutions A and B were mixed and 0.3% xanthan gum was added to make it up to 100L.

Use and dosage: for expelling and killing in vivo parasitic helminth and in vitro parasites in goats and sheep, 4ml thereof were administered per 10kg body weight.

Example 12

In this example, an oral composite formulation emulsion containing 1.5% of IVM and 30% of Albendazole was prepared.

1.66kg of IVM with a purity of 90% were weighed up and put into a dissolving jar to be dissolved by adding 18L of ethanol therein to obtain a solution A. Then 31.5kg of Albendazole with a purity of 95% were weighed up and dissolved in 5L of glacial acetic acid, and triethanolamine was used to adjust its pH value to 4 to 5, then 8kg of Tween-80 were added and mixed uniformly, and then 18kg of glycerine and 0.5kg of phenylmethanol were added to obtain a solution B, and the solutions A and B were mixed, then a solution of 2% sodium carboxymethycellulose was added in to make it up to 100L.

Use and dosage: for expelling and killing in vivo parasites (helminth) and in vitro parasites in goats and sheep, 1ml thereof was used per 75kg body weight.

Example 13

In this example, an injection composite formulation emulsion containing 0.1% of AVM and 5.0% of Albendazole was prepared.

0.11kg of AVM with a purity of 90% were weighed up and put into a dissolving jar to be dissolved by adding 5L of ethanol, to obtain a solution A. Then 5.5kg of Albendazole were taken and dissolved in 18L of glacial acetic acid, and triethanolamine was used to adjust its pH value to 4 to 5, then 8kg of Tween-80 were added and mixed uniformly, then 45kg of glycerine were added to obtain a solution B, and the solutions A and B were mixed, then a solution of 0.3% xanthan gum was added in to make it up to 100L.

Use and dosage: for expelling and killing in vivo parasitic helminth and in vitro parasites in goats and sheep, 2ml of the emulsion were injected per 10kg body weight.

Example 14

In this example, an injection composite formulation emulsion containing 1.2% of IVM and 24% of Albendazole was prepared.

1.33kg of IVM with a purity of 90% were weighed up and put into a dissolving jar to be dissolved by adding 48L of ethanol to obtain a solution A. Then 25.3kg of Albendazole with a purity

of 95% were weighed up and dissolved in 4L of glacial acetic acid, and triethanolamine was used to adjust its pH value to 4 to 5, then 2kg of Tween-80 were added and mixed uniformly, and then 8kg of glycerine were added to obtain a solution B, and the solutions A and B were mixed, then a solution of 2% sodium carboxymethycellulose was added in to make it up to 100L.

Use and dosage: for expelling and killing in vivo parasites (helminth) and in vitro parasites in goats and sheep, 1ml thereof was used per 60kg body weight.

Example 15

In this example, a composite formulation oily injection solution for injection use containing 0.1% of AVM and 5% of Albendazole was prepared.

5.5kg Albendazole were taken and added into 40L of sesame oil, which was ground in a bead mill until the Albendazole particles were smaller than 5μm to obtain an Albendazole oil suspension. Then 0.11kg of IVM with a purity of 90% were taken and dissolved in 2L of ethyl oleate, and then 30L of sesame oil was added and mixed uniformly, and this oil solution was mixed with the Albendazole oil suspension, and sesame oil was added to make it up to 100L which was ready for use.

Use and dosage: for expelling and killing in vivo parasitic helminth and in vitro parasites in goats and sheep, 1ml thereof was injected per 5kg body weight.

Example 16

In this example, a composite formulation oily injection solution for injection use containing 1.0% of IVM and 10% of Albendazole was prepared.

10.5kg of Albendazole with a purity of 95% were taken and added into 40L of sesame oil, which was ground in a bead mill until the Albendazole particles were smaller than 5μm to obtain an Albendazole oil suspension. Then 1.11kg of IVM with a purity of 90% were taken and dissolved in 10L of ethyl oleate, and then 30L of sesame oil were added and mixed uniformly, and this oil solution was mixed with the Albendazole oil suspension, and sesame oil was added to make it up to 100L.

Use and dosage: for expelling and killing in vivo parasites (helminth) and in vitro parasites in goats and sheep, 1ml thereof was used per 50kg body weight.

Example 17

This example is to compare the pharmacodynamic action of the composite formulation in the present invention with that of Avermectin, Ivermectin, and Albendazole used as single agents. Healthy animals were selected and divided into groups at random, and then the numbers of nematodes, cephalocysts and trematodes were counted according to a conventional counting method, and their parasite expelling rates were calculated separately.

Table 1 Effects of various preparations on in vivo helminth and in vitro acari in sheep.

Dosage forms	Dose (mg/kg)		parasite expelling rates (%)					
	AVM /IVM	ABDZ	Haemonchus contortus	T. colubriformis	Trichuris ovina	Moniezia	Fasciola hepatica	Psoroptes ovis
Oral powder of example 1	0.2	10	100	100	91.5	100	100	95.1
Avermectin powder	0.2	-	100	100	92.0	0	0	94.2
Capsules of example 3	0.2	10	100	100	90.5	100	100	93.6
Ivermectin capsule	0.2	-	100	100	90.2	0	0	93.5
Tablets of example 5	0.2	10	100	100	92.1	100	100	94.1
Albendazole tablet	-	15	100	100	89.7	100	100	0
Paste of example 7	0.2	10	100	100	90.7	100	100	94.4
Suspension of example 9	0.2	10	100	100	89.9	100	100	95.2
Oral emulsion of example 11	0.2	10	100	100	90.5	100	100	95.0
Injection emulsion of example 13	0.2	10	100	100	92.6	100	100	94.3
Oily injection of example 15	0.2	10	100	100	94.2	100	100	96.2

Note: the Avermectin powder was the commercial Avermectin powder (produced by New Technology Development Co., Ltd. of Beijing Agriculture University). The Ivermectin capsules were the commercial Ivermectin capsules (produced by New

Technology Development Co., Ltd of Beijing Agriculture University). The Albendazole tablets were the commercial product (produced by Wutianma Pharmaceutical Factory of Gansu Province).

It can be seen from the results of this example that when Avermectin or Ivermectin was mixed with Albendazole to form the composite formulation, it was capable of expelling and killing nematodes, cephalocysts and trematodes in vivo and acarids in vitro; while Avermectin and Ivermectin as single agents had no effect against cephalocysts and trematodes; Albendazole as single agent had no effect against acarids in vitro, so it is demonstrated that the composite formulation can expand the parasiticidal spectrum, so it reduces the dosage, and lowers the costs both in manufacture and application.